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9 MAR 2017

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Evaluation of XStat and Combat Gauze in a Swine Model of Lethal Junctional Hemorrhage in Coagulopathic Swine

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Abstract

Background

Hemorrhage is associated with the majority of potentially survivable deaths on the battlefield. Effective and field tested products are lacking to treat junctional and noncompressible injuries. XStat™ is a newly developed, FDA-approved product designed to treat junctional hemorrhage. The product is composed of mini sponges that expand on contact with blood to produce tamponade. The committee on tactical combat casualty care has recently approved the product for use as part of its treatment guidelines, but data is lacking to assess its efficacy in different wounding patterns and physiologic states.

Methods

Large (70-90kg) male swine were used in all experiments. Dilutional coagulopathy was induced by replacing 60% of the animal's estimated blood volume with room temperature Hextend™. Following dissection, isolation, and lidocaine incubation, uncontrolled hemorrhage was initiated by transection of both axillary artery and vein. Free bleed was allowed to proceed for 30 seconds until intervention with either XStat or Combat Gauze™ followed by standard backing. Primary outcomes were survival, hemostasis, and blood loss.

Results

Nineteen, healthy animals were entered into the study. XStat-treated animals achieved hemostasis in less time and remained hemostatic longer than Combat Gauze. Less blood was lost during the first 10 minutes following injury in the XStat group than the Combat Gauze group. However, no differences were observed between XStat-treated and Combat Gauze-treated groups based on survival. All animals died before the end of the observation period except one in the XStat-treated group.

Conclusions

The results presented here show XStat performed better than Combat Gauze in this model of junctional hemorrhage in coagulopathic animals. Continued testing and evaluation of XStat should be performed to optimize application and to determine appropriate indications for use.

Introduction

Traumatic hemorrhage, particularly when occurring on the torso, is responsible for the greatest number of potentially survivable deaths in recent conflicts.^{1,2} Fast, effective, and easily applied treatments for junctional and noncompressible hemorrhage are needed as treating these injuries proves challenging with current standards of care. Junctional tourniquets and resuscitative endovascular balloon occlusion of the aorta (REBOA) are promising new technologies.³⁻⁶ However, each has limitations that make them insufficient for some injury locations or wounding patterns. Junctional tourniquets are mainly effective when injuries are slightly distal to junction,⁷ while REBOA is more complex to implement and does not work for injuries of the upper torso.⁸ Hemostatic gauzes, including QuikClot Combat Gauze (CG; Z-Medica, Wallingford, CT), are effective in controlling hemorrhage in compressible sites, but do not offer definitive hemostasis.^{9,10} Therefore, the development and testing of new products in different wounding patterns and physiological states will improve point of care treatments.

XStat (Revmedx, Wilsonville, OR) is a newly developed hemostatic device designed to treat junctional wounds in the groin or axilla by the injection of self-expanding, mini-sponges directly into a bleeding wound. The device has been approved by the Food and Drug Association and is recommended by the Committee on Tactical Combat Casualty Care (CoTCCC) to control bleeding.^{11,12} It has been shown to be more effective than CG in a swine model of junctional hemorrhage.^{13,14} XStat also is applied significantly faster than standard gauze and produces pressure throughout a wound cavity in a simulated injury using ballistic gel.¹⁵

The aims of this study were to compare XStat to one of the CoTCCC standard of care for hemostatic dressings, CG. A junctional injury was created in coagulopathic swine prior to application of the test dressing. We hypothesized that XStat would be more effective in creating hemostasis due to less reliance on coagulation factors and also its ability to produce even pressure throughout a wound.

Materials and Methods

Overview

This study is a randomized, blinded, prospective trial. Male, Yorkshire-Landrace Swine, weighing 70 to 90 kg (John Albert Yorkshire Farm, Cibolo, TX) were entered into the experimental protocol. All subjects were treated according to *The Guide for the Care and Use of Laboratory Animals* (National Research Council, 1996). The study was approved by United States Air Force 59th Medical Wing's Institutional Animal Care and Use Committee. Animals were excluded from analysis when the subject died before treatment or a significant deviation from protocol occurred. An overview of the experimental protocol is shown in Figure 1.

Surgical Preparation

Animals were fasted overnight before surgery, but allowed free access to water. Animals were sedated with 4.4 mg/kg tiletamine-zolazepam IM and 2.2 mg/kg ketamine IM. Buprenorphine was then given for alleviation of pain at 0.01 mg/kg IM. Anesthesia was induced via mask with 2-4% Isoflurane in an air/oxygen mixture of 40-60%. Following intubation, isoflurane was adjusted to maintain a minimum alveolar concentration of 1.2 or greater.

Vascular access was obtained using modified Seldinger technique. The left external jugular vein was accessed for resuscitation fluids, and a pulmonary artery catheter (Edwards Life Sciences, Irvine, CA) was inserted via the right external jugular vein. The right carotid was accessed to monitor blood pressure and to allow for blood sampling. Splenectomy was performed through a midline laparotomy to prevent splenic autoperfusion during hemorrhage followed by a cystostomy for urine collection.

Induction of Coagulopathy

Induction of coagulopathy was performed according to previous studies.^{5,16} Briefly, 60% of the estimated blood volume was removed by the right femoral artery at 50 mL/min. Simultaneously, room temperature Hextend was infused at the same rate through the right external jugular vein. Hypothermia was allowed to progress until a temperature of 34.5°C was reached; subsequently, warming blankets were used to keep temperatures near 34.5°C until the injury phase.

Injury and Intervention

To gain access to the axillary artery and vein, a four cm incision was made parallel to the sternum over the pectoralis major muscle. The axillary artery, axillary vein, and brachial plexus were then minimally dissected away (~2 cm) from the surrounding tissue. Wound cavity volume was determined by measuring the amount of warmed saline necessary to fill the wound cavity. The vessels were then bathed in 2% lidocaine for ten minutes to induce dilation. After suction removal of lidocaine, a necropsy blade was used to transect both the axillary artery and vein to initiate injury (t=0). Hemorrhage was allowed to proceed for 30 seconds, while blood was collected by suction and weighed. The test hemostatic dressing was then applied to the wound using either a single roll of CG or up to four XStat applicators. Kerlix was packed into the wound as backing, but no manual compression was applied in either group. Hemostasis was defined as no blood leaving the wound cavity. Blood flowing from the wound was collected by suction following treatment in two phases: initial ten minutes and the remainder of the two-hour observation period.

Following injury, animals were given a 500 mL bolus of Hextend at 100 mL/min through the left external jugular vein. Following this bolus, up to 10 L of lactated Ringer's solution was administered at 100 mL/min to maintain a mean arterial pressure between 60 and 65 mmHg in keeping with previous similar studies.¹⁷ Death was defined as a mean arterial pressure (MAP) less than 20 mmHg and end-tidal CO₂ (EtCO₂) less than 15 mmHg maintained for two minutes. Animals were euthanized by an overdose of pentobarbital once death criteria was reached or when two hours had passed from the initial injury.

Outcomes and Analysis

The primary outcomes used in this study were survival, hemostasis, and blood loss. Secondary outcomes included hemodynamic parameters including heart rate (HR), MAP, EtCO₂, cardiac output (CO), central venous pressure (CVP), and mean pulmonary artery pressure (MPAP). Metabolic factors analyzed included lactate, base excess, pH, and, resuscitation fluids (lactated Ringer's solution, LRS) used to maintain MAP above 60.

Data is presented as mean \pm standard deviation unless otherwise noted. One way ANOVA was used for most analysis. However, Kruskal-Wallis ANOVA on ranks was used when normality test failed (if $p < 0.05$). Survival and hemostasis were analyzed using Fisher's exact test. Additionally, survival was analyzed by log-ranks analysis. Statistical analysis and data management were performed using Excel 2010 (Microsoft, Redmond, WA) and Sigmaplot 12 (Systat Software, San Jose, CA).

Results

Study Group Statistics

Nineteen animals weighing 75.9 ± 4.5 kg were included for analysis in this study: CG (10 animals) and XStat (9 animals). No differences were observed between groups with respect to baseline weight, MAP, MPAP, CVP, heart rate, or rectal temperature (Table 1). Four animals had to be excluded from the analysis: one animal died during coagulopathy and was not included in randomization, one animal from CG and one from XStat were excluded due to a protocol deviation of 45% oxygen during injury, and one animal randomized to XStat was excluded due to infusion pump failure.

Induction of Coagulopathy

The replacement of 60% estimated blood volume with Hextend resulted in the administration of 2962 ± 172 mL over 59.2 ± 3.5 minutes and the removal of 3004 ± 204 g of blood with no significant differences between groups (Table 1). Coagulopathy was observed by an increase in INR from 1.07 ± 0.05 to 1.45 ± 0.10 s ($p < 0.001$) with no significant differences between groups. Overall hemoglobin levels decreased from 10.0 ± 0.8 to 4.0 ± 0.4 g/dL ($p < 0.001$). Mild hypothermia was observed as rectal temperature decreased from 37.2 ± 0.5 at baseline down to $35.2 \pm 0.8^\circ\text{C}$ ($p < 0.001$) following induction of coagulopathy.

Injury

Prior to injury, animals had a MAP of 67.6 ± 8.4 mmHg with no significant differences between groups (Table 1). Cavity volumes were similar between groups with a volume of 104 ± 15 mL and 117 ± 33 mL for XStat and CG groups respectively ($p = 0.324$). Following complete transection of both axillary artery and vein, 862 ± 218 g of blood was lost after 30 seconds of free bleed with no significant differences between groups. At the end of the 30 second bleed, MAP was similar between groups and reached an average of 38.5 ± 6.9 mmHg with no significant differences between groups.

Hemostatic Dressing Performance

Hemostatic dressings were applied through the pool of blood at the wound site. Pack time, which includes total time for both the test dressing and Kerlix backing, was 16 seconds shorter with XStat than with CG (Table 2). The number of XStat applicators that was used varied from two to four with an average of 2.8 ± 0.8 applicators. One XStat applicator, out of 27 used, malfunctioned during application. The exact mechanism of failure was inconclusive and not determined to be user error or manufacturer's error.

The achievement of hemostasis was considered the primary outcome. Only one animal (XStat-treated) had hemostasis immediately following treatment. Nearly all XStat-treated animals achieved an eventual hemostasis, while less than half of CG did (Table 2). Of the animals that did reach hemostasis, the time that it took to achieve hemostasis was significantly shorter with XStat than CG ($p < 0.05$). Similarly, the total time where the animals survived while hemostatic was also significant when comparing XStat with CG ($p < 0.05$).

Following completion of packing, blood was collected and weighed. This shed blood was separated into the first ten minutes following packing (aka Platinum 10 minutes) and the rest of the observation period

(Table 2). During the platinum 10 minutes, CG-treated animals bled more than XStat-treated animals with the differences approaching significance ($p = 0.058$). However, total blood loss over the full two-hour observation period was not significantly different between groups.

Discussion

This study was performed to evaluate the efficacy of XStat in comparison to QuikClot Combat Gauze in a model of junctional hemorrhage, a leading cause of potentially survivable deaths on the battlefield. The hemostatic products were tested in a lethal model of axillary arterial and venous injury in the context of adult-sized (70-90 kg) swine with dilutional coagulopathy. Following treatment, the animals were resuscitated with a 500 mL bolus of Hextend followed by up to 10 L of lactated Ringer's solution to keep the mean arterial pressure between 60 and 65 mmHg and to follow the DoD's consensus model for evaluating hemostatic dressings.¹⁷

The results of this study show that XStat was more effective in reaching hemostasis, maintaining hemostasis, and had less bleeding the first 10 minutes after application. XStat also had a quicker application time confirming previous studies, but this study included both packing of backing and test dressing masking out differences between the two dressings. Despite these results, there were not any significant differences with regard to survival or time of death.

XStat-treated animals had significantly less blood loss than CG-treated animals during the first 10 minutes following injury. This period, "the platinum 10 minutes," was chosen *a priori* as an endpoint to illustrate differences between products during the critical period following trauma. This examination of the blood loss before any animal death offers a more complete comparison of dressing performance without the censor of data from animal death. Additionally, this 10 minute distinction has proven effective previously in similar product evaluation trials.¹⁰

There was not a direct relationship between achievement of hemostasis and survival in the data presented here. For example, animals that had relatively early hemostasis paradoxically did not survive the full observation period. Furthermore, animals that had little bleeding following dressing application still died. In fact, the animal that bled the least died the earliest in the XStat group. These contradictory results imply that the coagulopathy combined with the aggressive resuscitation paradigm was partly responsible for the high mortality rates and not solely due to dressing performance.

No manual pressure or pressure dressings were used in this study. Interestingly, a study performed by Navy researchers did not find any difference with or without manual pressure in a similar model of swine axillary injury (ref). Revmedx's XStat instructions are to "Cover the wound with an occlusive or pressure dressing. If available, use an elastic bandage. If bleeding persists, apply manual pressure until bleeding is controlled." Meanwhile, the QuikClot Combat Gauze instruction are to "apply pressure for 3 minutes or until bleeding stops. Wrap and tie bandage to maintain pressure." Standard gauze backing was used in these experiments to make the findings more generalizable to various wounding patterns.

There are limitations to this study including the lack of a defined correlation between hemostasis and survival mentioned above. The wound produced here was surgical in nature and likely does not reflect real world injury patterns. However, XStat is designed such that the small sponges can expand into any shaped cavity. Additionally, these experiments were performed in a controlled laboratory setting with relatively small sample sizes. Nevertheless, the results here produced statistically different results between the two products utilizing this junctional injury model.

Currently, XStat is recommended by the TCCC as "best for deep, narrow-tract junctional wounds".¹² Future studies may aim to expand the recommendation of the TCCC to allow for XStat to be applied to regions and circumstances outside junctional wounds such as the neck, abdomen, or pelvis. The product

could also be used in different situations outside of point-of-injury as was seen in the first combat casualty use. After failure to control intraoperative bleeding from a leg wound using cautery and hemostatic gauze, XStat was successfully used to stop the bleeding.¹¹

Conclusion

The CoTCCC recently added XStat to the list of approved hemostatic dressings. This work confirms this recommendation and provides new evidence of its efficacy in creating hemostasis to a rapidly bleeding wound. More research and field use will help confirm its place in point-of-injury care.

References (not all are in manuscript yet)

1. **Eastridge BJ, Mabry RL, Seguin P, et al.** Death on the battlefield (2001-2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg.* 2012;73:S431-437.
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Table 1. Pre Injury Characteristics

	Combat Gauze	XStat	<i>p</i> -value
Baseline			
Weight (kg)	76.3 ± 5.0	75.6 ± 4.1	0.745
MAP (mmHg)	60.4 ± 9.2	62.5 ± 10.4	0.654
MPAP (mmHg)	18.3 ± 1.6	18.7 ± 2.7	0.756
CVP (mmHg)	7.4 ± 1.9	7.2 ± 1.6	0.862
Heart Rate (bpm)	60.3 ± 7.2	55.0 ± 7.2	0.135
Temperature (°C)	37.3 ± 0.3	37.1 ± 0.7	0.710
Post Coagulopathy Induction			
Hextend Coagulopathy (mL)	2975 ± 192	2947 ± 159	0.728
Blood Removed (g)	2986 ± 198	3023 ± 222	0.704
INR	1.25 ± 0.05	1.28 ± 0.04	0.228
Hemoglobin (g/dL)	9.9 ± 0.6	10.1 ± 0.9	0.557
Temperature (°C)	35.2 ± 0.6	35.1 ± 1.0	0.841
Pre-injury MAP (mmHg)	68.7 ± 10.1	66.4 ± 6.4	0.574
Post-Injury/ Pre-Treatment			
Pre-treatment blood loss (g)	900 ± 242	763 ± 238	0.479
MAP at end of injury (mmHg)	38.9 ± 7.6	38.1 ± 6.4	0.538

MAP, Mean Arterial Pressure; MPAP, Mean Pulmonary Artery Pressure; CVP, Central Venous

Pressure; INR, International Normalized Ratio

Table 2. Post Intervention Data

	Combat Gauze	XStat	p-value
Application Time (s)	87.1 ± 17.4	71.5 ± 17.6	0.069
Immediate Hemostasis	0/10 (0%)	1/9 (11%)	0.474
Eventual Hemostasis	4/10 (40%)	8/9 (89%)	0.057
Time to Reach Hemostasis (min)	33.8 ± 4.8	20.3 ± 9.8	0.028*
Total Hemostasis Time (min)	5.4 ± 9.5	25.6 ± 31.3	0.029*
Time of Death (min)	35.4 ± 16.0	48.9 ± 29.1	0.438
First 10 minutes blood loss (g)	898 ± 705	461 ± 422	0.058
After 10 minutes blood loss (g)	312 ± 373	434 ± 435	0.377
Survival	0/10 (0%)	1/9 (11%)	0.474

*, $p < 0.05$

Figures

Figure 1. Experimental Schematic

Figure 1

